What is claimed is:

1.   A humanized antibody that binds specifically to human tissue factor (TF) to form a complex, wherein factor X or factor IX binding to the complex and the FX or FIX activation by TF:VIIa are inhibited.

2.   The humanized antibody of claim 1, wherein the antibody has a dissociation constant (K_d) for the TF of less than about 0.5 nM.

3.   The humanized antibody of claim 1 or 2, wherein the antibody is further characterized by increasing blood clotting time by at least about 5 seconds as determined by a standard prothrombin (PT) clotting assay at an antibody concentration of <15 nM.

4.   The humanized antibody of claim 1 or 2, wherein the antibody has a binding specificity for the TF about equal or greater than the antibody obtained from cell line H36.D2.B7 deposited under ATCC Accession No. HB-12255.

5.   The humanized antibody of claim 1 or 2, wherein the antibody has a binding affinity for the TF about equal to or greater than the antibody obtained from cell line H36.D2.B7 deposited under ATCC Accession No. HB-12255.

6.   The humanized antibody of claim 1 or 2, wherein the antibody comprises at least one fully murine complimentarity determining region (CDR).

7.   The humanized antibody of claim 1 or 6, wherein the antibody comprises at least one fully human framework (FR) region.

8.   The humanized antibody of claim 1, wherein the antibody has at least about 90% amino acid sequence identity to a human antibody.

9.   The humanized antibody of claim 1, wherein the variable region of the humanized antibody has at least about 70% amino acid sequence identity to a human antibody variable region.

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10.   The humanized antibody of claim 1, wherein each of frameworks (FRs) 1, 2, 3 and 4 has at least about 95% amino acid sequence identity to the light chain FR sequences shown in Figure 12A (SEQ ID NO. ___).

10   11.   The humanized antibody of claim 1, wherein the antibody comprises a light chain constant region having at least about 95% amino acid sequence identity to the sequence shown in Figure 14A or 15A (SEQ ID NO. ___).

12.   The humanized antibody of claim 1, wherein each of frameworks (FRs) 1, 2, 3 and 4 has at least about 95% amino acid sequence identity to the heavy chain sequences shown in Figure 13A (SEQ ID NO. ___).

13.   The humanized antibody of claim 12, wherein the antibody further comprises a heavy chain constant region having at least about 95% amino acid sequence identity to sequence
20   shown in Figure 14B or 15B (SEQ ID NO. ___).

14.   The humanized antibody of claim 1, wherein the antibody has an IgG1 (hOAT) or IgG4 (hFAT) isotype.

25   15.   A human TF binding fragment of the humanized antibody of claim 1.

16.   The human TF binding fragment of claim 15, wherein the fragment is Fab, Fab', or F(ab)$_2$.

17.   A humanized antibody comprising at least one murine complementarity determining region (CDR), wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor X or factor IX binding to TF or TF:FVIIa and activation by TF:FVIIa thereto is inhibited.

18.   The humanized antibody of claim 17, wherein all the CDR (light and heavy chain) are murine.

19.   The humanized antibody of claim 17, wherein the antibody further comprises as least one human framework (FR) region.

20.   The humanized antibody of claim 19, wherein the amino acid sequences of all the FR (light and heavy chain) are human or within 2 amino acid substitutions of being human.

21.   The humanized antibody of claim 17, wherein the first CDR (CDR1) of the heavy chain hypervariable region is at least 95% identical to the CDR1 amino acid sequence shown in Figure 13B (SEQ ID NO. ___).

22.   The humanized antibody of claim 17, wherein the second CDR (CDR2) of the heavy chain hypervariable region is at least 95% identical to the CDR2 amino acid sequence shown in Figure 13C (SEQ ID NO. ___).

23.   The humanized antibody of claim 17, wherein the third CDR (CDR3) of the heavy chain hypervariable region is at least 95% identical to the CDR3 amino acid sequence shown in Figure 13D (SEQ ID NO. ___).

24.   The humanized antibody of claim 17, wherein the first CDR (CDR1) of the light chain hypervariable region is at least 95% identical to the CDR1 amino acid sequence shown in Figure 12B (SEQ ID NO. ___).

25. The humanized antibody of claim 17, wherein the second CDR (CDR2) of the light chain hypervariable region is at least 95% identical to the CDR2 amino acid sequence shown in Figure 12C (SEQ ID NO. ___).

26. The humanized antibody of claim 17, wherein the third CDR (CDR3) of the light chain hypervariable region is at least 95% identical to the CDR3 amino acid sequence shown in Figure 12D (SEQ ID NO. ___).

27. The humanized antibody of claim 19, wherein the first framework (FR1) of the heavy chain hypervariable region is at least 95% identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___).

28. The humanized antibody of claim 27, wherein the FR1 comprises at least one of the following amino acid changes: E1 to Q; Q5 to V; P9 to G; L11 to V; V12 to K; Q19 to R; and T24 to A.

29. The humanized antibody of claim 19, wherein the second framework (FR2) of the heavy chain hypervariable region is at least 95% identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___).

30. The humanized antibody of claim 29, wherein the FR2 comprises at least one of the following amino acid changes: 41H to P; and 44S to G.

31. The humanized antibody of claim 19, wherein the third framework (FR3) of the heavy chain hypervariable region is at least 95% identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___).

32.   The humanized antibody of claim 31, wherein the FR3 comprises at least one of the following amino acid changes: 76S to T; 77T to S; 80F to Y; 82H to E; 84N to S; 87T to R; 89D to E; and 91S to T.

5   33.   The humanized antibody of claim 19, wherein the fourth framework (FR4) of the heavy chain hypervariable region is at least 95% identical to the amino acid sequence shown in Figure 13A (SEQ ID No. ___).

34.   The humanized antibody of claim 33, wherein the FR4 comprises the following amino

10   acid change: 113L to V.

35.   The humanized antibody of claim 19, wherein the first framework (FR1) of the light chain hypervariable region is at least about 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___).

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36.   The humanized antibody of claim 35, wherein the FR1 comprises at least one of the following amino acid changes: 11QL to L; 15L to V; 17E to D; and 18 to R.

37.   The humanized antibody of claim 19, wherein the second framework (FR2) of the light

20   chain hypervariable region is at least about 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___).

38.   The humanized antibody of claim 37, wherein the FR2 has the following amino acid changes: 37Q to L.

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39.   The humanized antibody of claim 19, wherein the third framework (FR3) of the light chain hypervariable region is at least about 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___).

40.   The humanized antibody of claim 39, wherein the FR3 has the following amino acid changes: 70K to D, 74K to T, 80A to P, 84A to V, and 85N to T.

41.   The humanized antibody of claim 40, wherein the fourth framework (FR4) of the light chain hypervariable region is at least about 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___).

42.   The humanized antibody of claim 41, wherein the FR4 comprises the following amino acid changes: 100A to Q; and 106L to I.

43.   A human TF binding fragment of the humanized antibody of claim 17.

44.   The human TF binding fragment of claim 43, wherein the fragment is Fab, Fab', or F(ab)$_2$.

45.   A humanized antibody comprising at least one murine complementarity determining region (CDR), wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor X or factor IX binding to TF or TF:FVIIa and activation by TF:FVIIa thereto is inhibited, the antibody comprising on the heavy chain:

   a) a first CDR (CDR1) which is at least 95% identical to CDR1 amino acid sequence shown in Figure 13B (SEQ ID NO. ___),

   b) a second CDR (CDR2) which is at least 95% identical to the CDR2 amino acid sequence shown in Figure 13C (SEQ ID NO. ___),

   c) a third CDR (CDR3) which is at least 95% identical to the CDR3 amino acid sequence shown in Figure 13D (SEQ ID NO. ___),

   d) a first framework (FR1) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO.___),

   e) a second framework (FR2) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

f) a third framework (FR3) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___), and

g) a fourth framework (FR4) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID No. ___);

46. The antibody of claim 45 further comprising on the light chain,

h) a first CDR (CDR1) which is at least 95% identical to CDR1 amino acid sequence shown in Figure 12B (SEQ ID NO. ___),

i) a second CDR (CDR2) which is at least 95% identical to the CDR2 amino acid sequence shown in Figure 12C (SEQ ID NO. ___),

j) a third CDR (CDR3) which is at least 95% identical to the CDR3 amino acid sequence shown in Figure 12C (SEQ ID NO. ___),

k) a first framework (FR1) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

l) a second framework (FR2) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

m) a third framework (FR3) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___), and

n) a fourth framework (FR4) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID No.___).

47. The antibody of claim 45 further comprising the light chain constant sequence of Figure 14A (SEQ ID No. ___) or Figure 15A (SEQ ID No. ___)_

48. The antibody of claim 45 further comprising the heavy chain constant region of Figure 14B (SEQ ID No. ___) or Figure 15B (SEQ ID No. ___).

49. A human TF binding fragment of the humanized antibody of claim 45.

50.   The human TF binding fragment of claim 45, wherein the fragment is Fab, Fab', or F(ab)$_2$.

51.   A humanized antibody comprising on the heavy chain:

        a) a first CDR (CDR1) identical to the CDR1 amino acid sequence shown in Figure 13B (SEQ ID NO. ___),

        b) a second CDR (CDR2) identical to the CDR2 amino acid sequence shown in Figure 13C (SEQ ID NO. ___),

        c) a third CDR (CDR3) identical to the CDR3 amino acid sequence shown in Figure 13D (SEQ ID NO. ___),

        d) a first framework (FR1) identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___),

        e) a second framework (FR2) identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___),

        f) a third framework (FR3) identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___); and

        g) a fourth framework (FR4) identical to the amino acid sequence shown in Figure 13A (SEQ ID No. ___); and

        on the light chain:

        h) a first CDR (CDR1) identical to CDR1 amino acid sequence shown in Figure 12B (SEQ ID NO. ___),

        i) a second CDR (CDR2) identical to the CDR2 amino acid sequence shown in Figure 12C (SEQ ID NO. ___),

        j) a third CDR (CDR3) identical to the CDR3 amino acid sequence shown in Figure 12D (SEQ ID NO. ___),

        k) a first framework (FR1) identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

        l) a second framework (FR2) identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

m) a third framework (FR3) identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___), and

n) a fourth framework (FR4) identical to the amino acid sequence shown in Figure 12A (SEQ ID No. ___).

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52.   The antibody of claim 51 further comprising the light chain constant sequence of Figure 14A (SEQ ID No. ___) or Figure 15A (SEQ ID No. ___).

53.   The antibody of claim 51 further comprising the heavy chain constant sequence of

10   Figure 14B (SEQ ID No. ___) or 15B (SEQ ID No. ___).

54.   The humanized antibody of claim 51, wherein the antibody has an IgG1 or IgG4 isotype.

15   55.   A human TF binding fragment of the humanized antibody of claim 4.

56.   The human TF binding fragment of claim 55, wherein the fragment is Fab, Fab', or F(ab)$_2$.

20   57.   The humanized antibody of claim 1, wherein the antibody is a monoclonal antibody.

58.   A single-chain antibody comprising the hypervariable region of the antibody of claim 1.

59.   An isolated nucleic acid encoding at least one of the heavy or light chain of the

25   humanized antibody of claim 1.

60.   A recombinant vector comprising the isolated nucleic acid of claim 59.

61.   A host cell comprising the recombinant vector of claim 60.

62.   A composition comprising the humanized antibody of claim 1, and at least one pharmaceutically acceptable carrier.

5   63.   A method of inhibiting blood coagulation in a mammal, the method comprising administering to the mammal an effective amount of the humanized antibody of claim 1 or fragment thereof that binds specifically to human tissue factor (TF) to form a complex, wherein factor X or factor IX binding to TF or TF:FVIIa and activation by TF:FVIIa thereto is inhibited, the method further comprising forming a specific complex between the antibody and

10   the TF to inhibit the blood coagulation.

64.   A method of inhibiting blood coagulation in a mammal, the method comprising administering to the mammal, an effective amount of the humanized antibody of claim 7 comprising at least or fragment thereof, wherein the antibody or fragment binds specifically to

15   human tissue factor (TF) to form a complex, and further wherein factor X or factor IX binding to TF or TF:FVIIa and activation by TF:FVIIa thereto is inhibited, the method further comprising forming a specific complex between the antibody and the TF to inhibit the blood coagulation.

20   65.   A method of inhibiting blood coagulation in a mammal, the method comprising administering to the mammal, an effective amount of a humanized antibody or fragment thereof wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor X or factor IX binding to TF or TF:FVIIa and activation by TF:FVIIa thereto is inhibited, the antibody or fragment comprising on the heavy chain:

25   a) a first CDR (CDR1) which is at least 95% identical to CDR1 amino acid sequence shown in Figure 13B (SEQ ID NO. ___),

                b) a second CDR (CDR2) which is at least 95% identical to the CDR2 amino acid sequence shown in Figure 13C (SEQ ID NO. ___),

c) a third CDR (CDR3) which is at least 95% identical to the CDR3 amino acid sequence shown in Figure 13D (SEQ ID NO. ___),

d) a first framework (FR1) which is at least 95% identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___),

e) a second framework (FR2) which is at least 95% identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___),

f) a third framework (FR3) which is at least 95% identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___),

g) a fourth framework (FR4) which is at least 95% identical to the amino acid sequence shown in Figure 13A (SEQ ID No. ___);

and on the light chain,

h) a first CDR (CDR1) which is at least 95% identical to CDR1 amino acid sequence shown in Figure 12B (SEQ ID NO. ___),

i) a second CDR (CDR2) which is at least 95% identical to the CDR2 amino acid sequence shown in Figure 12C (SEQ ID NO. ___),

j) a third CDR (CDR3) which is at least 95% identical to the CDR3 amino acid sequence shown in Figure 12D (SEQ ID NO. ___),

k) a first framework (FR1) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

l) a second framework (FR2) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

m) a third framework (FR3) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

n) a fourth framework (FR4) which is at least 95% identical to the amino acid sequence shown in Figure 12A (SEQ ID No. ___),

o) a light chain constant region which is at least 95% identical to the amino acid sequence shown in Figure 14A (SEQ ID No. ___) or Figure 15A (SEQ ID No. ___), and

p) a heavy chain constant region which is at least 95% identical to the amino acid sequence shown in Figure 14B (SEQ ID No. ___) or Figure 15B (SEQ ID No. ___).

66.   A method of inhibiting blood coagulation in a mammal, the method comprising administering to the mammal, an effective amount of a humanized antibody or fragment thereof wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor X or factor IX binding to TF or TF:FVIIa and activation by TF:FVIIa thereto is inhibited, the antibody or fragment comprising on the heavy chain:

a) a first CDR (CDR1) identical to CDR1 amino acid sequence shown in Figure 13B (SEQ ID NO. ___),

b) a second CDR (CDR2) identical to the CDR2 amino acid sequence shown in Figure 13C (SEQ ID NO. ___),

c) a third CDR (CDR3) identical to the CDR3 amino acid sequence shown in Figure 13D (SEQ ID NO. ___),

d) a first framework (FR1) identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___),

e) a second framework (FR2) identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___),

f) a third framework (FR3) identical to the amino acid sequence shown in Figure 13A (SEQ ID NO. ___),

g) a fourth framework (FR4) identical to the amino acid sequence shown in Figure 13A (SEQ ID No. ___);

and on the light chain:

h) a first CDR (CDR1) identical to CDR1 amino acid sequence shown in Figure 12B (SEQ ID NO. ___),

i) a second CDR (CDR2) identical to the CDR2 amino acid sequence shown in Figure 12C (SEQ ID NO. ___),

j) a third CDR (CDR3) identical to the CDR3 amino acid sequence shown in Figure 12D (SEQ ID NO. ___),

k) a first framework (FR1) identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

l) a second framework (FR2) identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

m) a third framework (FR3) identical to the amino acid sequence shown in Figure 12A (SEQ ID NO. ___),

n) a fourth framework (FR4) identical to the amino acid sequence shown in Figure 12A (SEQ ID No. ___),

o) a light chain constant region which is identical to the amino acid sequence shown in Figure 14A (SEQ ID No. ___) or Figure 15A (SEQ ID No. ___), and

p) a heavy chain constant region which is identical to the amino acid sequence shown in Figure 14B (SEQ ID No. ___) or Figure 15B (SEQ ID No. ___).

67.   A method of detecting tissue factor (TF) in a biological sample, the method comprising contacting a biological sample with the antibody of claim 1 under conditions conducive to forming a complex and detecting the complex as being indicative of the TF in the biological sample.

68.   A method for producing the humanized antibody of claim 1, wherein the method comprises providing a host cell transformed with either 1) a first expression vector encoding the light chain of the humanized antibody or fragment thereof and a second expression vector encoding the heavy chain of the humanized antibody or fragment thereof, or 2) a single expression vector encoding both the light chain and the heavy chain of the humanized antibody or fragment thereof, maintaining the host cell under growth conditions in which each chain is expressed; and isolating the humanized antibody or fragment thereof.

69.   A method for producing a humanized antibody, wherein the method comprises:

a) comparing the amino acid sequence of a light chain framework from a rodent antibody against a collection of corresponding human antibody framework sequences,

b) selecting a human framework sequence from the collection having the greatest amino acid sequence identity to the corresponding rodent light chain framework,

c) mutagenizing a DNA segment encoding the rodent light chain framework to encode a humanized light chain framework having an amino acid sequence that is substantially identical to the human framework sequence selected in step b),

d) repeating steps a) thru c) for each individual framework of the rodent light chain to produce a plurality of DNA sequences in which each sequence encodes a humanized light chain framework, wherein each of the corresponding human framework sequences selected in step b) are from the same or different human antibody,

e) assembling into a first vector encoding at least the light chain variable region of the rodent antibody, the DNA sequences encoding the humanized framework sequences produced in step d); and

f) introducing the assembled vector into a host under conditions sufficient to produce the humanized antibody.

70. The method of claim 69, wherein the method further comprises:
g) comparing the amino acid sequence of a heavy chain framework from the rodent antibody against a collection of corresponding human antibody framework sequences,

h) selecting a human framework sequence from the collection having the greatest amino acid sequence identity to the corresponding rodent heavy chain framework,

i) mutagenizing a DNA segment encoding the rodent heavy chain framework to encode a humanized heavy chain framework having an amino acid sequence that is substantially identical to the human framework sequence selected in step h); and

j) repeating steps g) thru i) for each individual framework of the rodent heavy chain to produce a plurality of DNA sequences in which each sequence encodes a humanized heavy chain framework, wherein each of the corresponding human framework sequences selected in step h) are from the same or different human antibody.

71.   The method of claim 70, wherein the method further comprises assembling into a second vector encoding at least the heavy chain variable region of the rodent antibody, the DNA sequences encoding the humanized framework sequences produced in step j); and introducing the assembled first and second vectors into a host under conditions sufficient to produce the humanized antibody.

72.   The method of claim 70, wherein the method further comprises assembling into the first vector encoding at least the light chain variable region of the rodent antibody, the DNA sequences encoding the humanized framework sequences produced in step j); and introducing the assembled first vector into a host under conditions sufficient to produce the humanized antibody.